VARIATIONS IN PATHOGENIC ACTIVITY AMONG TUBERCLE BACILLI

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VARIATIONS IN PATHOGENIC ACTIVITY AMONG TUBERCLE BACILLI.[1]

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In the production of states of disease due to infection we should recognize two main modifying factors — the pathogenic activity or virulence of the infecting organism, and the resistance[2] of the infected individual.

Variations in the pathogenic power of bacteria are probably the result of prolonged sojourn in slightly different environments. If, for instance, a given tubercle bacillus had successfully invaded a vigorous adult, and had successfully passed from this person to a second, a third, or a long series of vigorous adults, and had then after this prolonged contact with tissues of a certain vitality invaded the body of a child, we are justified in assuming that the virulence of this bacillus with reference to the child has been increased by its successful invasion of vigorous, naturally more resistant adults. Again, if a tubercle bacillus, vegetating in a tuberculous lesion of the skin, through a favorable combination of accidents had produced a series of infections of the skin, we may assume that differences, however slight, between this bacillus and one infecting a series of lungs would become eventu-

[1] Presented, by invitation, at the meeting of the American Climatological Association, September 1, 1898.

[2] This term figures in medical writings chiefly as immunity, although the term is merely relative, since there is no absolute immunity.

ally established. A continuation of such series, through fortuitous circumstances, might finally produce two varieties of tubercle bacilli, each incapable of taking the other's place successfully. It is probably in some such way as this that varieties are produced which become restricted as to the territory they are capable of infecting, while at the same time they become especially adapted to infect this restricted territory. The bacillus of bovine tuberculosis illustrates another phase of the same problem. Does it by its continued passage through the bovine body become more virulent to human beings, or does it thereby lose largely its power to graft itself upon the human system? Either alternative may be true, but neither is proven.

I cite these illustrations to emphasize the relativity of the term virulence and its dependence on the character of the host, as well as the relativity of the term resistance, as it depends more or less on the bacterium. These two terms, virulence and resistance, may be compared to the two opposite sides of the same shield. They are, as mathematicians would say, functions of one another. They are, however, none the less real when we come to deal with given species, races or types of individuals whom the tubercle bacillus may infect. It takes a long time to modify bacteria, and for the short space of life of the individual their characters are practically fixed. We need here a certain sense of perspective to enable us to appreciate the slow change during long periods of time and the temporary fixity. The evolution of new characters is going on in all living organisms, but all our information concerning them is anchored, as it were, to their temporary stability.

In the laboratory we are able to modify experimentally both the virulence of certain bacteria and the resistance of the host. By passing these bacteria through

a long series of susceptible animals of the same species a greatly increased potency of the bacteria, with reference to that species, is noticed at the end. By treating susceptible animals with certain bacterial products or cultures killed by heat or chloroform the resistance may be increased. Different degrees of induced resistance lead to different clinical and pathological types of the same inoculation disease, so that the etiological relationship between them would hardly be surmised without a definite knowledge of the experimental details.[3]

Variations in the pathogenic activity have been demonstrated for a considerable number of disease-producing species. In fact, it seems to be the rule to encounter slight variations in the study of series of cultures of the same organism obtained from different sources. I might cite many illustrations in support of these statements, but I shall limit myself to one of general interest. The diphtheria bacillus, which is so well characterized by the production of a specific toxin, may vary in the power to produce this toxin from case to case. Thus bacilli from one source have produced for years just three times the amount of toxin produced by bacilli from another source, when cultivated in bouillon of the same composition. Other numerical relations in the power of toxin production may be cited, but the fact I wish to emphasize is the constancy of the variation under identical conditions.

In their contact with infectious diseases physicians have laid the emphasis now on virulence, now on resistance. With diseases having a rapid course, like

[3] I have expressed this relationship between the type of disease on the one hand and the virulence and resistance on the other by the simple equation $d = \frac{v}{r}$ where v = virulence, r = resistance. Increasing v or diminishing r we augment the severity of the disease (d). Increasing r or diminishing v we diminish its severity.

cholera, the plague and diphtheria, the relative resistance of individuals is in the background, and the virulence of the infecting agent receives more attention. With diseases of slow progress, like tuberculosis, attention is centred upon the resisting capacity of the individual as expressed by heredity, bodily conformation and environment — the soil, in other words, of which we have heard so much. It may be that the instinct of the experienced physician is quite correct in attributing to the resisting capacity of the individual in the more prolonged chronic infections a more conspicuous influence than in the acute infections, because in the former the latent forces of resistance have had time to develop in the course of the disease. Of these two conceptions, virulence and resistance, I shall confine my remarks to the most neglected one — not for the purpose of bringing to light startling hypotheses or unlooked-for facts, but to call attention to virulence as an element not to be ignored in our study of tuberculosis.

Variations in pathogenic activity among bacteria specifically related may be due to artificial cultivation, or they may be found spontaneously, and they are then due to a natural cultivation in the human or animal body through long periods of time. There are on record some statements concerning the weakening or attenuation of the tubercle bacillus after prolonged artificial cultivation, which I may pass over here, as it is the fate of all bacteria to become reduced in virulence in this way. There are also some statements concerning artificial attenuation with disinfectants, like iodoform. These do not bear on the main question before us, which is concerned with the discovery of varieties of tubercle bacilli as they actually occur in the diseased body. These may be found infecting different species of animals, or they may be looked for

in individuals of the same species. These distinctions will be better understood if we glance for a moment over the large field occupied by this formidable organism.

It is now a widely-known fact that, besides man, the lower animals are the victims of tuberculosis. Tuberculosis of cattle is a widespread evil, increasing year by year. Through the food products derived from cattle swine have become extensively infected in some countries. Carnivora and especially monkeys contract it. It is rarely found in horses. Poultry in European countries is subject to it. Maffucci has shown that the bacillus producing tuberculosis in fowls has certain characteristics which distinguish it from the human bacillus, and which give it the rank of a variety or race. Investigations which I have been carrying on during the past three years have revealed certain constant differences between bacilli obtained from human sputum and those from cattle, sufficient, in my estimation, to make the bovine bacillus a race by itself.[4] It is probable that the tubercle bacillus has become modified, through a long series of transfers, from one animal to another of the same species into a number of varieties, which may be considered more or less adapted to their respective hosts, but whose relation to other hosts is at present obscure. The relation, for instance, in which the bovine tubercle bacillus stands to the human race is of the utmost importance, in view of the wide dissemination of this disease and the difficulties encountered in coping with it.

Passing to the disease as it is found in the human subject, we are confronted by the problem of variation in a narrower sense. It is evident that differences in pathogenic power are much less likely to become evolved in bacteria which are parasitic upon individuals of the same species because of a close uniformity

[4] The Journal of Experimental Medicine, iii (1898), p. 451.

of soil, and if they occur at all, the differences are probably less appreciable than those occurring in different species.

In weighing the probabilities in favor of the existence of varieties among human tubercle bacilli, we find a strong argument in the wide divergence of occupation and environment into which the life of the human race has become differentiated. This is not so with domestic animals, cattle for example, which, with slight variations in food and the amount of indoor confinement, are doomed to the same monotonous existence. In the human race the great differences in the condition of individuals have provided for infectious agents a variety of soils in which to vegetate. If through chance several given bacilli should invade series of the different types of individuals, slight differences in the bacilli might eventually be looked for. Such differences may, however, be too slight to be apprehended with our present crude methods. In the paper referred to above I called attention to the probable modifying influence upon the tubercle bacillus of a prolonged multiplication in the necrotic material and the bronchial exudation in cases of mild, long-standing pulmonary tuberculosis. Here a contact with living tissue endowed with bactericidal properties does not occur, and the tubercle bacilli live a saprophytic existence, which must sooner or later modify their aggressiveness towards living tissue.

Speculations and hypotheses are, however, of little value, often positively injurious unless in part supported by demonstrable facts. Hence they must be tested by experiment upon animals and observation of animal diseases in which secondary influences are less numerous and preponderant than in man. The broader and more varied these experiments and observations are the safer the conclusions when applied to

human diseases. A survey of the field of experimental medicine shows that but little has been as yet accomplished in the study of variations of the tubercle bacillus, mainly because it seems to have been taken for granted that varieties do not exist. In his investigations upon the new tuberculin Koch [5] had occasion to have a number of cultures studied by his assistants, and in his report he briefly states that there was considerable variation in the virulence.[6]

To Arloing of Lyons belongs the credit of having called attention to this subject more than ten years ago. He and his pupils have been experimenting with the products of various forms of tuberculosis in man, and as a result of their experiments they claim that with rare exceptions the bacilli of pulmonary tuberculosis are more virulent than those of the scrophulous or surgical forms of tuberculosis.[7] Arloing bases his claim upon the fact that bacilli from visceral tuberculosis are much more pathogenic towards rabbits than those of the scrophulous forms. When, according to this author, bits of tuberculous tissue or sputum are placed in the subcutaneous tissue of the thigh of rabbits, those from the pulmonary disease invade the lungs of rabbits, where tubercles may be detected after two months. Those from the other types of tuberculosis fail to reach the lungs and remain localized. In guinea-pigs both produce eventually a generalized disease.

In a recent paper, Courmont and Denis,[8] two of Arloing's pupils, continuing his work, have shown that the pulmonary form of tuberculosis may now and then harbor quite attenuated bacilli.

[5] Deutsche med. Wochenschr. 1897, No. 14.

[6] Since the completion of this paper this work has been published in detail by Vagedes (Zeitschr. für Hygiene, xxviii, 1898, p. 276).

[7] Leçons sur la Tuberculose et Certaines Septicémies. Paris, 1892.

[8] De la Tuberculose Pulmonaire à Bacilles Atténués, Rev. de la Tuberculose, v (1897), p. 289.

Arloing has encountered considerable opposition, mainly because the method he employed is not above criticism. It is a well-known fact that the course of the disease, artificially induced in animals with tubercle bacilli, depends largely upon the number of bacilli introduced. Inasmuch as they greatly vary in number in different lesions, and as the staining does not tell us whether they are living or dead, the inoculation of the products of disease is a rather uncertain factor upon which to base conclusions.

In order to test Arloing's work, Auclair [8] recently undertook, under Grancher's supervision, the study of cultures from four cases of tuberculosis — a rapidly progressive tuberculosis of a gland of the neck and a case each of true scrophula, slow phthisis, and acute meningitis. On guinea-pigs the intra-abdominal injection of the cultures had nearly the same effect. Hence, the author does not hesitate to regard them as identical in virulence. Auclair in failing to test the cultures upon rabbits did not improve much upon the method of Arloing, for with the aid of these animals we are enabled to determine degrees of virulence not recognizable in the very susceptible guinea-pig. The views of Arloing are therefore still to be disproved. They are, however, quite in harmony with facts obtained experimentally with other pathogenic bacteria to which I have already referred. It is quite impossible, from our present standpoint, to consider the great variations in the localization of the tubercular virus, and in the course taken by it in the human body, as merely fortuitous. Undoubtedly the factors of virulence and resistance play a prominent part. We are in a much better position to-day to undertake investigations into the relative virulence of tubercle

[8] Recherches sur la Virulence des Bacilles Tuberculeux Humains provenant de Sources Cliniques Diverses, Arch. de Méd. Exp., ix (1897) p. 1124.

bacilli from different sources than into the much more complex factor of resistance to their invasion and multiplication. Any light thrown on the subject of virulence will indirectly illumine that of resistance or susceptibility.

My own studies of human tubercle bacilli, though somewhat limited in range, lead me to believe in the existence of minor variations in the form of the bacillus, the appearance and character of the cultures and the virulence, whose significance needs still to be deciphered. Among seven cultures of bacilli from sputum, one differed from all the rest in refusing to grow satisfactorily upon dog's serum. Of other forms of this disease only one culture has been under observation. The patient, sixty-five years old, had a large swelling on the left side of the neck, which broke and discharged much pus. It continued discharging through sinuses until death, which took place about five months after the appearance of the swelling. When first seen by the pathologists of the Boston City Hospital, to whom I am indebted for the material, the discharge contained a very large number of bacilli. It was supposed that these were of more than the average virulence, but the cultures which I obtained through guinea-pigs proved rather the opposite. They were less virulent than the sputum cultures studied, both toward rabbits and guinea-pigs. This case illustrates the uncertainty of our deductions, when the pathogenic agent is not studied independently of the many modifying influences at work in the human body.

It would be presumptuous on my part to dilate upon the practical value of a more accurate knowledge of tubercle bacilli. Those who are engaged in pathological, etiological and therapeutic studies of tuberculosis will promptly discern how such information will serve their special purposes. To the student of etiology

the search for the bovine variety of the tubercle bacillus in the human body will for a time be the most important problem. To the pathologist, the variation in the lesions produced by the tubercle bacillus will need renewed study by comparing the bacilli which are responsible for divergent tissue changes. The physician will desire better information upon the possible differences between bacilli producing tuberculosis of the integuments, of the bones and joints, and of the viscera. He will wish to know any demonstrable differences between a rapidly fatal case and one that is protracted over years. He will above all wish to interpret his therapeutic successes and failures.

The outcome of studies of the pathogenic power of tubercle bacilli upon animals must, however, not be taken too literally. It should be borne in mind that results are at best only comparative. Thus increased virulence toward certain species of animals, as tested in the laboratory, must not be interpreted to mean necessarily increased virulence towards the human organism, although this may eventually be proved to be the case. The only positive information we may safely accept are the accurately ascertained degrees of difference among tubercle bacilli from different sources, as expressed in terms of bacteriology. Thus I have calculated approximately that the virulence of sputum bacilli to bovine bacilli is as 1 to 20 or 1 to 30 when tested on rabbits. No one will venture to assert with these figures in mind that when these races are implanted in the human body this great difference will be wiped out and the resulting disease be the same. Such differences signify certain unknown differences in behavior in the human body, which must be studied by the clinician and the pathologist before they can become available as positive knowledge.